

Contents

Chapter 1	Malaria: New Medicines for its Control and Eradication	1
	<i>Timothy N. C. Wells and Winston E. Gutteridge</i>	
1.1	Introduction	1
1.2	The Challenges of the Different <i>Plasmodium</i> Species	2
1.3	Currently Available Antimalarials	3
1.4	Resistance	9
1.5	Drugs for <i>Plasmodium vivax</i>	11
1.6	Prophylaxis	15
1.7	Development Challenges	15
1.8	The Next Generation of Antimalarials: Developing a Target Product Profile	16
1.9	Finding New Molecules: Genes and Screens	19
1.10	Eradication: Moving Beyond the Erythrocytic Stages	22
1.11	The Malaria Research Pipeline	23
1.12	Conclusions	25
	Acknowledgements	26
	References	26
Chapter 2	Semisynthetic Artemisinin and Synthetic Peroxide Antimalarials	33
	<i>Leann Tilley, Susan A. Charman and Jonathan L. Vennerstrom</i>	
2.1	Semisynthetic Artemisinins	33
2.1.1	Discovery of Artemisinin, Mechanism of Action, and SAR	33
2.1.2	Artemisinin Combination Therapy (ACT)	37

2.1.3	Pharmacokinetic Properties	37
2.1.4	Toxicity	38
2.1.5	Potential Drug Resistance	38
2.2	Investigational Semisynthetic Artemisinins and Synthetic Peroxides	39
2.2.1	Introduction	39
2.2.2	Artelinic Acid	39
2.2.3	Artemisone	40
2.2.4	Arteflene	43
2.2.5	Fenozan B07	46
2.2.6	Arterolane	48
2.2.7	PA1103/SAR116242	51
2.2.8	RKA182	54
2.3	Conclusions	56
2.4	Abbreviations	56
	Acknowledgements	56
	References	57

Chapter 3 Antimalarial Agents Targeting Nucleotide Synthesis and Electron Transport: Insight from Structural Biology **65**
Margaret A. Phillips

3.1	Introduction	65
3.2	Electron Transport – the bc1 Complex	68
3.2.1	Atovaquone and Mechanism of Resistance to bc1 Inhibitors	68
3.2.2	Next-generation bc1 Complex Inhibitors	70
3.3	Pyrimidine Nucleoside and Nucleotide Metabolism	72
3.3.1	Dihydrofolate Reductase (DHFR) – Therapeutically used Inhibitors and Structural Basis of Resistance	72
3.3.2	Structure-based Design of Next-generation DHFR Inhibitors	74
3.3.3	Other Targets in Pyrimidine and Folate Metabolism	76
3.4	<i>De novo</i> Pyrimidine Biosynthesis	76
3.4.1	Dihydroorotate Dehydrogenase (DHODH) as a New Drug Target	76
3.4.2	Identification of Novel Inhibitors: Triazolopyrimidines	77
3.4.3	Insights from X-ray Structural Analysis of DHODH Bound to Inhibitors	78
3.5	Purine Salvage Enzymes	79
3.5.1	Purine Nucleoside Phosphorylase	80
3.5.2	Other Purine Salvage Enzymes	82

<i>Contents</i>	xiii
3.6 Conclusions	82
Acknowledgements	83
References	83
Chapter 4 Human Targets Repositioning and Cell-based Approaches for Antimalarial Discovery	88
<i>Arnab K. Chatterjee and Elizabeth A. Winzeler</i>	
4.1 Introduction	88
4.2 Human Targets Classes as a Source for Antimalarials	89
4.2.1 Farnesyltransferase Inhibitors	89
4.2.2 HDAC Inhibitors	92
4.2.3 Kinase Inhibitors	94
4.2.4 Protease Inhibitors	97
4.2.5 Folate Biosynthesis	100
4.2.6 Future Perspectives on Target-based Discovery using Novel Hit-finding Methods	101
4.3 Phenotypic Drug Discovery	102
4.3.1 Overview of Cell-based Assays and Drug Discovery	102
4.3.2 Lab-evolved Resistance and Genome-scanning for Target Discovery	104
4.4 Conclusions	106
References	107
Chapter 5 The Medicinal Chemistry of Eradication: Hitting the Lifecycle where it Hurts. Approaches to Blocking Transmission	112
<i>Jeremy Nicholas Burrows and Robert Edward Sinden</i>	
5.1 Introduction	112
5.2 Features of <i>Plasmodium</i> Biology Relevant to Drug Design	113
5.3 Status of Current Biological Assays and Future Needs	115
5.3.1 Pre-erythrocytic (Liver-stage) Assays	115
5.3.2 Asexual Blood-stage (Schizonticide) Assays	116
5.3.3 Mature Gametocyte (Gametocytocide) Assays	116
5.3.4 Mosquito-stage Assays (Gametogenesis; Ookinete and Oocyst Formation)	117
5.4 Clinical Aspects of Transmission-blocking Approaches	118
5.4.1 Development of Transmission-blocking Drugs	120

5.5	Medicinal Chemistry Perspectives on Transmission	
	Blocking	120
5.5.1	Liver-stage Parasites	120
5.5.2	Gametocyte-stage Parasites	124
5.5.3	Vector-stage Parasites	126
5.6	Conclusions	128
	Acknowledgements	129
	References	129
Chapter 6	Drugs for Kinetoplastid Diseases – Current Situation and Challenges	134
	<i>Simon L. Croft</i>	
6.1	Introduction	134
6.2	Leishmaniasis	135
6.2.1	Visceral Leishmaniasis	136
6.2.2	HIV/Leishmaniasis Co-Infections	141
6.2.3	Cutaneous Leishmaniasis (CL)	142
6.3	Human African Trypanosomiasis	145
6.4	South American Trypanosomiasis (Chagas Disease)	150
6.5	Conclusions	152
	References	153
Chapter 7	Drug Discovery for Kinetoplastid Diseases	159
	<i>Robert T. Jacobs</i>	
7.1	Introduction	159
7.2	Background Biology and Genetics	160
7.3	Identification of Parasitocidal Compounds through Whole-cell Assays	160
7.3.1	Benzoxaboroles	160
7.3.2	Lipophilic Amines	161
7.3.3	Nitroheterocycles	162
7.3.4	Metal-based Parasiticides	163
7.4	Polyamine Pathway	164
7.4.1	Ornithine Decarboxylase (ODC)	165
7.4.2	S-Adenosylmethionine Decarboxylase (SAM-DC, AdoMet-DC)	166
7.4.3	Spermidine Synthase (SpdSyn)	167
7.4.4	Trypanothione Synthetase (TrpSyn)	167
7.4.5	Trypanothione Reductase (TrpRed)	168
7.5	Energy Metabolism	168
7.5.1	Hexokinase (HK)	169
7.5.2	Phosphoglucose Isomerase (PGI) and Phosphofructokinase (PFK)	169

7.5.3	Fructose-1,6-Bisphosphate Aldolase	171
7.5.4	Phosphoglycerate Kinase (PGKB)	171
7.5.5	Phosphoglycerate Mutase (PGAM), Enolase and Pyruvate Kinase (PyK)	171
7.6	Lipid Biosynthesis and Utilization	172
7.6.1	Fatty Acids	172
7.6.2	Sphingolipids	173
7.6.3	Isoprenoids	174
7.6.4	Sterol Biosynthesis	175
7.7	Signal Transduction Pathways	176
7.7.1	Phosphodiesterases	176
7.7.2	Kinases	177
7.7.3	Proteases	178
7.8	Nucleic Acids	179
7.8.1	Purine Uptake and Metabolism	179
7.8.2	DNA Topoisomerases	181
7.8.3	DNA Binding Agents – Diamidines	182
7.9	Tubulin	183
7.10	Conclusions	184
	References	184
Chapter 8	The Challenges of Flavivirus Drug Discovery	203
	<i>Pei-Yong Shi, Qing-Yin Wang and Thomas H. Keller</i>	
8.1	Introduction	203
8.2	Flaviviral Diseases	204
8.3	Anti-flavivirus Strategies	205
8.4	Inhibition of Viral Proteins	206
8.4.1	NS3 Protease	206
8.4.2	NS3 Helicase	211
8.4.3	NS5 Polymerase	212
8.4.4	NS5 Methyltransferase	216
8.5	Host Targets	218
8.5.1	Host Targets Required for Viral Replication	218
8.5.2	Host Targets Involved in Disease Exacerbation	220
8.6	Cell-based Screening and Optimization	221
8.7	Conclusions	222
	References	223
Chapter 9	Current Approaches to Tuberculosis Drug Discovery and Development	228
	<i>Mark J. Mitton-Fry and Debra Hanna</i>	
9.1	The Global Problem of Tuberculosis and Current State of Affairs	228

9.2	The Preclinical Path to Developing New Agents	231
9.3	<i>In Vitro</i> Assays	235
9.3.1	Minimum Inhibitory Concentration Susceptibility Testing	235
9.3.2	Models for Assessing Activity Against Non-replicating Bacteria	236
9.3.3	Wayne Model of Oxygen Depletion	237
9.3.4	Loebel Model of Nutrient Depletion	238
9.3.5	Additional <i>In Vitro</i> Models	238
9.4	Mammalian Cell-based <i>In Vitro</i> and <i>Ex Vivo</i> Assays	238
9.4.1	Intracellular Infection Models	238
9.4.2	Macrophage Assays	239
9.4.3	Whole Blood Bactericidal Assay	239
9.5	Resistance Profiling	240
9.6	<i>In Vitro</i> PK-PD Hollow Fiber Systems	240
9.7	<i>In Vivo</i> Infection Models	242
9.7.1	Murine Models	242
9.7.2	Other <i>In Vivo</i> Species	248
9.8	Clinical Testing of Novel Therapies for TB	250
9.8.1	Phase 1 Trials	250
9.8.2	Phase 2a trials: Early Bactericidal Activity	251
9.8.3	Phase 2b Trials	252
9.9	Conclusions	252
	Acknowledgement	253
	References	253
Chapter 10	Diarrhoeal Diseases	262
	<i>David Brown</i>	
10.1	Disease Burden	262
10.1.1	Morbidity and Mortality Rates	262
10.1.2	Geography of Diarrhoeal Diseases	263
10.1.3	Pathogenic Organisms Causing Diarrhoeal Diseases	265
10.2	Prevention of Diarrhoeal Diseases	266
10.2.1	Hygiene, Sanitation and Public Health Policy	266
10.2.2	Breast-feeding and Micro-nutrient Supplementation	267
10.2.3	Vaccines	267
10.3	Treatment of Diarrhoeal Diseases	269
10.3.1	WHO Treatment Guidelines Summary	269
10.3.2	Oral Rehydration Salts	270
10.3.3	Zinc	271
10.3.4	Antibiotics	272
10.3.5	Anti-protozoals	275

<i>Contents</i>	xvii
10.3.6 Antisecretories	277
10.3.7 Antivirals	282
10.3.8 Other drugs	282
10.4 Conclusions	283
References	286
Chapter 11 Anthelmintic Discovery for Human Infections	290
<i>Timothy G. Geary and Noelle Gauvry</i>	
11.1 Introduction and Background	290
11.2 Nematodes	291
11.2.1 Areas of Concern	294
11.2.2 Areas of Concern for Filarial Nematodes	298
11.3 Trematodes	298
11.3.1 Areas of Concern	301
11.4 Cestodes	302
11.4.1 Areas of Concern	303
11.5 Late-stage Anthelmintic Leads	303
11.5.1 Emodepside	303
11.5.2 Tribendimidine	305
11.5.3 Flubendazole	305
11.5.4 Moxidectin	306
11.5.5 Monepantel	307
11.5.6 Derquantel	307
11.5.7 <i>Bacillus Thuringiensis</i> (Bt) toxins	308
11.5.8 Closantel	308
11.5.9 Schistosomes	308
11.5.10 Cestodes	310
11.6 New Anthelmintic Leads	310
11.6.1 Monepantel Analogs	311
11.6.2 Closantel Analogs	311
11.6.3 Aminocyclohexanol Derivatives	311
11.6.4 Oxadiazole N-oxide Derivatives	312
11.7 Drug Discovery and Development: Pathways and Problems	312
11.8 Conclusions	314
References	314
Chapter 12 Managing the HIV Epidemic in the Developing World – Progress and Challenges	322
<i>Elna van der Ryst, Michael J Palmer and Cloete van Vuuren</i>	
12.1 The HIV Epidemic	322
12.1.1 HIV Transmission	323
12.1.2 The Global Spread of HIV Infection	323

12.1.3	HIV-1 Structure and Variability	325
12.1.4	Pathogenesis and Clinical Manifestations of HIV Infection	325
12.2	HIV-1 Replication and Development of Antiretroviral Drugs	328
12.2.1	HIV-1 Entry and Inhibitors of Virus Entry	329
12.2.2	Reverse Transcription and Reverse Transcriptase Inhibitors	334
12.2.3	Integration of Proviral DNA and Integrase Inhibitors	338
12.2.4	Production and Maturation of Progeny Virions and Inhibitors of Viral Protease	339
12.2.5	Ongoing Challenges – Managing Adverse Effects and Drug Resistance	340
12.3	Current State of the Art in the Management of HIV-1 Infection	343
12.3.1	Management of HIV Infection in Paediatric Patients	345
12.3.2	Prevention of Mother to Child Transmission	345
12.4	Universal Access to Antiretroviral Drugs – What are the Challenges?	346
12.4.1	Key Challenges for HIV Treatment in the Developing World	347
12.4.2	Optimisation of Antiretroviral Drugs for Developing Countries	348
12.5	Antiretroviral Drugs and Prevention of HIV-1 Infection – Future Directions	349
12.5.1	Pre-exposure Prophylaxis Using Oral Antiretroviral Therapy	350
12.5.2	Microbicides	350
12.5.3	Potential of Large Scale Treatment Programmes to Reduce Transmission	352
12.6	HIV Vaccine Development – Progress and Challenges	352
12.6.1	Requirements for Vaccine-induced Immune Responses	353
12.6.2	Candidate Vaccine Approaches	353
12.6.3	Progress to Date	354
12.7	Conclusions	355
	References	356

Chapter 13 Drug Discovery for Lower Respiratory Tract Infections	366
<i>J Carl Craft</i>	
13.1 Introduction	366
13.1.1 The Economics of Antibiotics: Getting a Return on Investment	367
13.1.2 Regulatory Uncertainty for Antibiotic Trials	368
13.2 Lower Respiratory Tract Infections Indications	369
13.2.1 Community-acquired Pneumonia	369
13.2.2 Hospital-acquired (Nosocomial) Pneumonia	370
13.2.3 Aspiration Pneumonia	371
13.2.4 Chronic Lung Infections: Abscess, Empyema, Bronchiectasis	372
13.2.5 Acute Bronchitis	372
13.2.6 Chronic Bronchitis Including Acute Bacterial Exacerbations of Chronic Bronchitis	372
13.3 Anti-infective Drug Research and Development	373
13.3.1 Classes of Antibiotics Important in Lower Respiratory Tract Infections	373
13.3.2 Target-based Synthetic Antimicrobials Important to Lower Respiratory Tract Infections	389
13.3.3 Antifungals	393
13.3.4 Antivirals	394
13.3.5 Emerging Classes of Potential Antimicrobials	397
13.4 Affordable Medicines for Lower Respiratory Tract Infections in the Least Developed Countries	398
13.5 Conclusions	401
References	401
Subject Index	412

